REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 21-48 and 50-55 are pending in this application. Claims 35-48, 51, 54, and 55 have been withdrawn as being drawn to a non-elected invention. Claim 21 has been amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Upon entry of these amendments, claims 21-34, 50, 52, and 53 will be pending and under active consideration.

b. Amendment to the Claims

Claim 21 has been amended to be directed in part to an isolated first viral nucleic acid or complement thereof wherein the first viral nucleic acid consists of 15-24 nucleotides and a second viral nucleic acid consisting of 50 to 131 nucleotides comprises the first viral nucleic acid…wherein the first and second viral nucleic acid are isolated from the genome of a virus. Withdrawn claim 35 has been similarly amended. Support for amended claims 21 and 35 can be found throughout the specification including the sequence listing, paragraphs 3 and 4 on page 4, and paragraph 4, page 5.

c. Request of Rejoinder

On page 2 of the Office Action, the Examiner withdrew newly added claims 54 and 55 as allegedly being drawn to the nonelected invention due to its dependency upon withdrawn claim 35. As stated previously with claim 35, upon allowance of the generic claim 21, Applicant will request rejoinder to Group II as well as SEQ ID NOS: 1-2078 and 2080-3353.

d. Double Patenting

On pages 8, 9, and 11-13 of the Office Action, claims 21-23, 25, 27, 28, 30-34, 52, and 53 are provisionally rejected under nonstatutory obviousness-type double patenting rejections. Specifically, claims 21-23, 25, 27, 28, 33 and 34 are provisionally rejected over claims 34-37 of U.S. Patent App. No. 10/707,003. Claims 21-23, 25, 27, 28, 33 and 34 are provisionally rejected over claims 23, 36, 39 of U.S. Patent Appl. No. 10/604,943. Claims 21-23, 25, and 30-34 are provisionally rejected over claims 22, 34, and 46 of U.S. Patent Appl. No. 10/604,943. Claims 52 and 53 are provisionally rejected over claims 21 and 23 of U.S. Patent Appl. No. 10/604,943. Claims 52 and 53 are provisionally rejected over claims 34 and 35 of U.S. Patent Appl. No. 10/707,003. Claims 52 and 53 are provisionally rejected over claims 21 and 51 of U.S. Patent Appl. No. 10/604,984. Claims 52 and 53 are provisionally rejected over claims 17 and 18 of U.S. Patent Appl. No. 10/708,952.

Claims 52 and 53 are provisionally rejected over claims 26 and 35 of U.S. Patent Appl. No. 10/709,739. Claims 52 and 53 are provisionally rejected over claims 20 and 22 of U.S. Patent Appl. No. 11/511,035.

Applicant respectfully requests that the Examiner hold the rejection in abeyance until there is allowable subject matter, at which time Applicant will consider the claims in U.S. Patent Appl. Nos. 10/707,003, 10/604,943, 10/604,984, 10/708,952, and 10/709,739, or file a terminal disclaimer.

2. Patentability Remarks

a. 35 U.S.C. §112, First Paragraph, Written Description

On pages 3, 4, 9, and 10 of the Office Action, the Examiner rejects claims 21-34, 50, 52 and 53 under 35 U.S.C. §112, first paragraph, for allegedly lacking proper written descriptive support. Specifically, the Examiner asserts that no single miRNA disclosed in the specification fully satisfies the "amended claimed" miRNA nucleotide. The Examiner further states that even if the specification adequately disclosed a single miRNA nucleotide sequence that satisfies all the claimed limitations, the single disclosed species is not representative of the broad genus of the claimed nucleotide. Applicant respectfully disagrees.

The instant application discloses the first miRNAs isolated from a virus with the disclosure of 8328 distinct miRNA sequences from a total of 584 different viral species. Each one of these viral miRNAs share common attributes and features that are recited in the claims. Specifically, each miRNA is a short nucleic acid (element (a) of claim 20) between 15 and 24 nucleotides. Each miRNA is derived from a larger precursor nucleic acid (element (b) of claim 20) between 50 and 131 nucleotides. In the processing of each miRNA, the precursor forms a stem and loop hairpin structure (element (c) of claim 20). The loop of the hairpin is between 3 and 19 nucleotides and the stem segments are between 14 and 71 nucleotides and between 30.8% and 100% complementary. Finally, each miRNA is capable of binding to a target mRNA (element (d) of claim 20) and inhibiting expression of a protein encoded by the target mRNA (element (e) of claim 20).

Elements (a), (b) and (c) recite ranges for certain features of the miRNA and the miRNA precursor. The boundaries for each of these ranges have been chosen from the specification such that each and every one of the 8328 disclosed miRNAs is included in the claim. Choosing the lowest and the highest values of these recited ranges from the disclosed miRNAs of the instant application is permissible because one of ordinary skill in the art would consider the claimed ranges

to be inherently supported by the discussion in the original disclosure (See MPEP §2165.05III). As a result, the Examiner is incorrect to state that the elements are based on "picking and choosing." If that were the case, at least one of the disclosed miRNAs would be excluded from the claim. That is not the case and the Examiner has impermissibly failed to take into account the inherent support of the claimed ranges.

Similarly, the Examiner is incorrect to state that no single miRNA fully satisifies the claimed nucleic acid. As mentioned above, each and every one of the 8328 disclosed miRNAs is encompassed by the claimed nucleotide. Finally, it is also erroneous for the Examiner to allege that the 8328 disclosed species are not representative of the claimed genus. Applicant is unsure what would be representative in this case if 8328 species from 584 different viral species were not considered representative.

In view of the foregoing, Applicant submits that the claimed genus is satisfied due to sufficient description of a representative number of species in the specification. Accordingly, Applicant submits that the rejection of claims 21-34, 50, 52 and 53 under 35 U.S.C. §112, first paragraph, for allegedly lacking proper written descriptive support, has been overcome and requests withdrawal of the rejection.

b. 35 U.S.C. §102(e), Anticipation

On pages 4-7 of the Office Action, the Examiner rejects claims 21, 22, 25, 33, 34 and/or 50 under 35 U.S.C. §102(e) as being anticipated by Zamore (U.S. Patent App. Pub. No. 2006/0009402; hereafter "Zamore"), Cullen et al. (U.S. Patent Appl. Pub. No. 2004/0053411; hereafter "Cullen"), and Khvorova et al. (U.S. Patent Appl. Pub. No. 2007/0031844; hereafter "Khvorova"). Specifically, the Examiner states in each rejection of the claims over Zamore, Cullen and Khvorova that "viral nucleic acid" is interpreted as a nucleic acid that targets and modulates viral nucleic acids when the claims are given its broadest reasonable interpretation. Therefore, the Examiner concludes that the claimed nucleic acids are not required to be viral and therefore are anticipated by Zamore, Cullen and Khvorova. In view of the foregoing amendment, Applicant respectfully submits that the amendments made herein overcome the rejection.

As stated above, the claimed nucleic acids are amended to be isolated from the genome of a virus. Specifically, independent claim 20 and its dependents 22, 25, 30 (probe), 34 (vector) and 50 are now directed in part to an isolated first viral nucleic acid (miRNA) or complement thereof wherein the first viral nucleic acid consists of 15-24 nucleotides and the second viral nucleic acid

(hairpin) consists of 50 to 131 nucleotides comprising the first viral nucleic acid …wherein the first and second nucleic acid are isolated from the genome of a virus. The claimed invention clearly requires that the claimed miRNA and hairpin related nucleic acids be isolated from a viral genome. In stark contrast, none of the sequences described in Zamore, Cullen, or Khvorova are viral miRNA sequences or would produce a viral miRNA sequence, and accordingly are not isolated from viral genomes. In view of the foregoing amendment and remarks, Applicant submits that the rejection of claims 20, 22, 25, 30, 34 and/or 50 under 35 U.S.C. §102(e) over Zamore, Cullen or Khovorova has been overcome and should be withdraw .

c. 35 U.S.C. §103(a), Obviousness

On page 7 of the Office Action, the Examiner maintains the rejection of claims 21-34 and 50 under 35 U.S.C. §103(a) as being obvious over Ambros *et al.*, *Cell* 107:823-826 (2001; hereafter "Ambros"), in view of Lai *et al*, *Genome Biology* 4:R42 (2003; hereafter "Lai"), and Knipe *et al.*, 76:4534-4538 (1979; hereafter "Knipe"). Applicant respectfully disagrees.

The Examiner has presented two sets of references over three different office actions as a basis of the obviousness rejection.[1] Specifically, the Examiner asserts that it would be expected to find miRNAs in other organisms besides complex eukaryotes (citing Lagos-Quintana and Ambros)[2] using computational methods or algorithms for predicting and verifying hairpins and their miRNAs (citing Moss, Konings, Grad, and Lai),[3] and these sequences could be identified in viruses since genomes and secondary structure in viruses existed at the time of filing (citing Knipe and Yu).[4] In response, Applicant has repeatedly presented compelling evidence that all the prior art miRNA sequences at the time of filing were evolutionary related within a few branches of the phylogenic tree[5] and the cited computational method art relies on this same sequence conservation for identifying additional miRNAs. The Examiner has failed each time to provide any concrete

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[1] Moss *et al.*, *Current Biology* 12:R138-R140 (2002); Konings *et al.*, *Journal of Virology* 66:632-640 (1992), Grad *et al.*, *Molecular Cell* 11:1253-1263 (2003) and Lai.

[2] Lagos-Quintana *et al.*, *Science* 294:853-858 (2001) and Ambros

[3] Moss *et al.*, *Current Biology* 12:R138-R140 (2002); Konings *et al.*, *Journal of Virology* 66:632-640 (1992), Grad *et al.*, *Molecular Cell* 11:1253-1263 (2003) and Lai.

[4] Knipe and Yu et al., J. of Virology 73:3638-3648 (1999).

[5] The Examiner has only provided prior art that demonstrates identification of miRNAs in a limited number of complex eukaryotes such as vertebrate (human, mice and rats), invertebrate animals (C. elegans, Drosophila) and plants) at the time of filing.

evidence that bridges the phylogenic gap between the cited prior art's identification of miRNAs within a few small branches of the phylogenic tree and the more divergent branches of the phylogenic tree representing single cell organisms (such as bacteria or yeast), acellular organisms (such as fungi) and viruses. Without this evidence, Applicant submits one of skill in the art at the time of filing would not reasonably expected success in identifying viral miRNAs from the teachings of the cited art.

Yet, here again in the current Office Action, the Applicant is face again with nearly the same obviousness rejection by the Examiner as the previous office action without any concrete evidence to bridge the phylogenic gap between what the prior art taught as known or predictable miRNAs vs. identified miRNAs in either single cell organisms or viruses themselves. Specifically, the Examiner dismisses the Applicant's argument by simply stating that it was known in the art that miRNAs exist in various organisms (refer to teachings of Ambros) and it was expected in the art that more miRNAs would be discovered in many other genomic sequences due to the rapid development and advancement in bioinformatics tools for identifying miRNA sequences for any known genomic sequence (refers to teachings of Lai et al). The Examiner concludes that since miRNAs were being discovered not only in a simple organism *C. elegans*, but in different organisms as the miRNA research field progressed as evidenced by Ambros, and bioinformatics was available under Lai, one of ordinary skill in the art **with creativity** would have reasonably expected that miRNAs likely would be present in the viral genome.

The obviousness standard is based upon predictability of the teachings of the prior art would reasonably lead one of skill to identify the claimed miRNAs and one of skill would expect success. This level of predictability is missing from the Examiner's presented arguments. Specifically, the Examiner has failed to note that even the "simple" worms (*C. elegans*) and flies (Drosophila) are genetically similar enough that these family of invertebrate eukaryotes are clustered within the same branches of the phylogenic tree as complex eukaryotes such as vertebrates (humans, mice and rats) and plants. These organisms, however, are so genetically divergent from single cell organisms such as bacteria and yeast, acellular organisms such as fungi, or viruses that their vicinity (multicell vs. single cell/viral) to each other in the phylogenic tree is completely separate and unclustered. The Examiner's prior art references of Ambros and Li do not overcome this gap between single cell organisms/viruses and multicell eukaryotes. Ambros only focuses of the identification of miRs in the multicell eukaryotes (i.e., worms, flies, vertebrates, plants) and at best, only states miRs could be discovered in "other" multicell eukaryotic organisms since no miRs were known to exist in singe cell

organisms or viruses at the time Ambros was published. Lai's miRNA seeker program, like the computational tools taught in Moss, Grad, and Konings, only rely of miRNA sequences conserved across bilaterian evolutionary related species and is therefore only applicable to higher multicellar organism such as worms, flies, and human. All of these computational tools for predicting miRs were based at the time of filing on a limited number of eukaryotic sequences (i.e., worm, flies, vertebrates and plants) and provide no guidance as to generating predictive algorithms for the divergent single cell organism (bacteria, yeast) or viral genomic sequences. Applicant submits that in view of the Examiner's failure to fill this phylogenic gap with evidence of miRNAs or tools for how to predict miRNAs in single cell organism/viruses, the cited prior art of record would not have led one of skill to a predictable conclusion of the claimed invention.

In addition, the Examiner has never addressed Applicants argument regarding the fact that one of skill in the art would not have expected viruses to contain miRNAs and hairpin precursors because viral genomes are too small and have little intergenic space to harbor hairpin precursors at a spacial frequency thought necessary at the timing of filing.[6] In view of the fact that miRNAs had only been isolated from species who are clustered within one region of the phylogenic tree completely divergent from viruses, the lack of predictive miRNA algorithm tools to account for viral genomic sequences, and doubts regarding the genome size vs. hairpin frequency necessary to harbor hairpin precursors in a viral genome, one of skill would not reasonably be able to predict the claimed invention and expect to succeed in identifying viral miRNAs at the timing of filing.

With regard to the Examiner's statement that one of skill with creativity would have reasonably expected that miRNAs would be present in viral genomic sequences, Applicant agrees only to the point that it would take creativity for one of skill to discover the claimed invention, but the level of creativity would have to be so high as to go beyond the level of predictability required by the obviousness standard and rather move to the point of being inventive as accomplished by the Applicants, not the prior art. As stated above, the mental bridge from complex eukaryotes computation models for predicting miRNAs in complex eukaryotes to identifying miRNAs in viruses based on Applicant's teachings was simply not present in the art at the time to filing. One of skill would have to be so creative as to be inventive because there was no reasonable expectation at the time of filing that miRNAs would be present in the viral genome. Applicant's extensive record as discussed above demonstrates this unpredictability, and the Examiner has failed to bridge the gap

[6] As discussed on pages 13-16 of Applicant's response dated February 26, 2008, less than one hairpin precursor would be expected for each viral organism due to small genome size and lack of intergenic space.

between the fatal divergence of sequence conservation between viruses and complex eukaryotes. In view of the foregoing, the Applicant respectfully asserts that one of skill with creativity would not have expected to be able to identify the claimed viral miRNAs and hairpins. Accordingly, Applicant submits that the rejection of claims 21-34 and 50 under 35 U.S.C. §103(a) as being obvious over Ambros Lai and Knipe has been overcome and should be withdrawn.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

POLSINELLI SHUGHART PC

Dated: November 6, 2009

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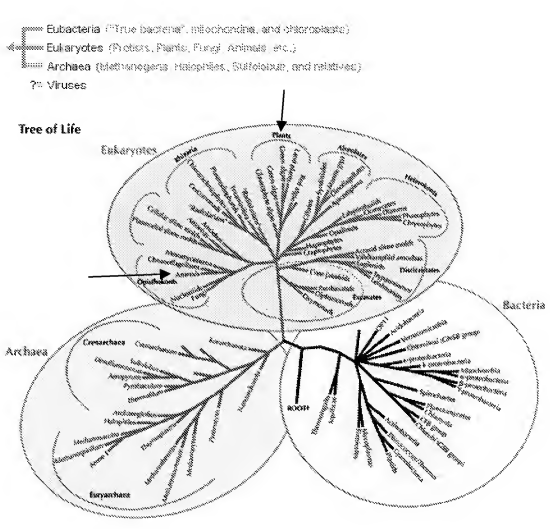
APPENDIX A


Eubacteria ("True bacteria", mitochondria, and chloroplasts)
Eukaryotes (Protists, Plants, Fungi, Animals, etc.)
Archaea (Methanogens, Halophiles, Sulfolobus, and relatives)
?= Viruses
Tree of Life
Eukaryotes
Plants
Alveolates
Heterokonts
Opisthokonts
Dictyostelids
Excavates
Bacteria
Archaea
Crenarchaea
ROOT
Euryarchaea